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CLINICAL CASE REPORT

Long-term follow-up of two patients with oligocone trichromacy

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Abstract
Introduction Oligocone trichromacy (OT) is an uncommon cone dysfunction disorder, the mechanism of which remains poorly understood. OT has been thought to be non-progressive, but its long-term visual outcome has been seldom reported in the literature. Our aim was to present two OT patients followed at our institution over 18 years.
Materials and methods Complete ocular examination, color vision, visual fields, and full-field electroretinography (ERG) were performed at initial presentation and follow-up. Spectral-domain optical coherence tomography (OCT) was performed during follow-up when available at our institution.
Results Initial ocular examination showed satisfactory visual acuities with normal fundus examination and near-to-normal color vision. However, computerized perimetry demonstrated a ring-shaped scotoma around fixation, and ERG showed a profound cone dysfunction. The discrepancy between preserved color vision and profound cone dysfunction leads to the diagnosis of OT. Subsequent follow-ups over 18 years showed subtle degradation of visual acuities along with progression of the myopia in both patients and slight worsening of color vision in one patient. Initial OCT revealed a focal interruption of the ellipsoid line along with decreased thickness of the perifoveal macula. Subsequent OCT imaging performed 2 years later did not show any macular changes.
Conclusion Although OT is known to be a non-progressive cone dysfunction, our results suggest that subtle degradation of the visual function might happen over time.

Keywords Oligocone trichromacy · Achromatopsia · Bradyopsia · Electroretinography · ERG · OCT

Introduction

Oligocone trichromacy (OT) is an uncommon non-progressive cone dysfunction disorder, described initially by Van Lith [1]. Patients with OT usually present with visual impairment, mild photophobia, normal fundus appearance, and profound cone dysfunction (oligocone), though color vision remains paradoxically within normal limits (trichromacy). Although OT has been thought to be non-progressive, little is known regarding its visual outcome.

In the present report, we describe the clinical, ERG, and OCT features of two patients with OT followed over an 18-year period of time.

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Patients and methods

Our retrospective study was approved by our institutional review board and fulfilled the tenets of the Declaration of Helsinki. Two sisters (patient 1, 16-year-old; patient 2, 11-year-old at initial presentation) were referred to our department in 1994 for unexplained, long-standing visual impairment with mild photophobia. Neither reported problems with dark–light adaptation or impaired movement perception.

Clinical data, including best-corrected visual acuities (BCVA), intraocular pressures, slit lamp and dilated fundus examinations, and eye movements, were collected.

Visual-field analysis included automated perimetry (Moniteur Ophtalmologique® using a 76-point standard algorithm, Metrovision, Perenchies, France). Color vision tests were performed using confusion tests (Ischihara 15-number plate) and ranking pigment tests (15 Hue of Farnsworth, 15 Desaturated Hue of Lanthony, 100 Hue of Farnsworth, and a New Color Test of Lanthony derived from Munsell). Spectral-domain optical coherence tomography (SD-OCT) of the macula was performed with Zeiss Cirrus HD-OCT (Carl Zeiss Meditec, Jena, Germany). Fundus imaging was performed with a Canon CF-60 UVi Fundus Camera (Canon USA Inc., New York).

Full-field electroretinograms (ERG) were recorded from both eyes following the standards of International Society of Clinical Electrophysiology of Vision (ISCEV) [2, 3]. The recording electrode was a Dencott® corneal contact lens placed after local anesthetic application (0.4 % oxybuprocaine) and corneal protection by a 0.5 % methylcellulose solution. The silver-chloride reference electrode was placed on the ipsilateral temple, and the ground electrode was positioned on the forehead. The pupils were dilated with 1 % tropicamide. Full-field electroretinography was performed using a Ganzfeld stimulator of the MonColor® unit (Metrovision, Perenchies, France). Dark-adapted ERG responses (rod response, maximal response) were obtained after 20 min of dark adaptation and light-adapted responses (cone response, 30-Hz flicker, ERG ON–OFF) after 10 min of light adaptation to the background luminance of 22 cd/m^2. The strength of standard flash (maximal response, cone response, and 30-Hz flicker) was 2.4 cd s/m^2, and the strength of attenuated dark-adapted flash (rod response) was 0.01 cd s/m^2. ERG ON–OFF was obtained with broadband white stimulus (1.7 log cd s/m^2) on a white background (40 cd/m^2). Dim red flash dark-adapted ERG was obtained with a 0.164 cd s/m^2 stimulus of 630 nm. To screen for recovery of a photoreceptoral function, we used a double-flash protocol: Two standard flashes of 2.4 cd s/m^2 were applied under dark-adapted condition with a variation of interstimulus interval from 20 to 45 ms. The interval between two pairs of flashes was always >120 s. All responses were differentially amplified and stored on the hard disk of a computer.

Genetic testing for achromatopsia (CeGaT GmbH, Tübingen, Germany) included bidirectional sequencing of the coding regions and intron–exon boundaries of CNGA3, CNGB3, GNAT2, PDE6C, and KCNV2 genes.

Results

Initial visit

Figure 1 shows the pedigree. There was no family history of visual impairment or co-sanguinity. At initial presentation, case 1's BCVA was 0.8 in the right eye (OD) and 0.9 in the left eye (OS) with −3.50 and −3.00 diopter lens, respectively, and case 2's BCVA was 0.4 OD and 0.5 OS with −1.50 and −2.00 diopter lens, respectively. Slit lamp and fundus examinations were unremarkable. Both patients were orthophoric in primary position and in all eccentric gazes with full extraocular motility and no nystagmus.

Color vision using saturated color tests was normal in both patients, but revealed subtle color discrimination problems on those using desaturated colors. Initial

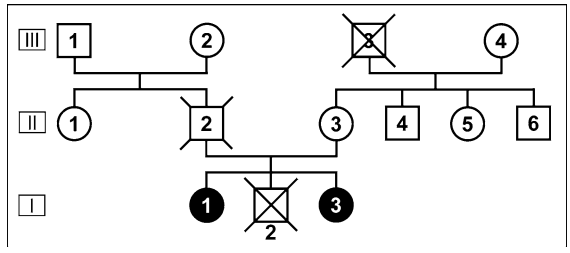

Fig. 1 Pedigree of patients 1 and 2. I1 and I3: probants; I2: DiGeorge syndrome; II2: died in a car accident; II1, II3, III2: seen at our institution, normal ocular examination

Table 1 Evolution of Farnsworth 100 Hue error score

Year of examination	Patient 1			Patient 2		
	OD	OS	AMNS	OD	OS	AMNS
1997	163	128	50–80	Not realized		
2010	216	156	48–75	75	167	50–80

AMNS, age-matched normal score [4]

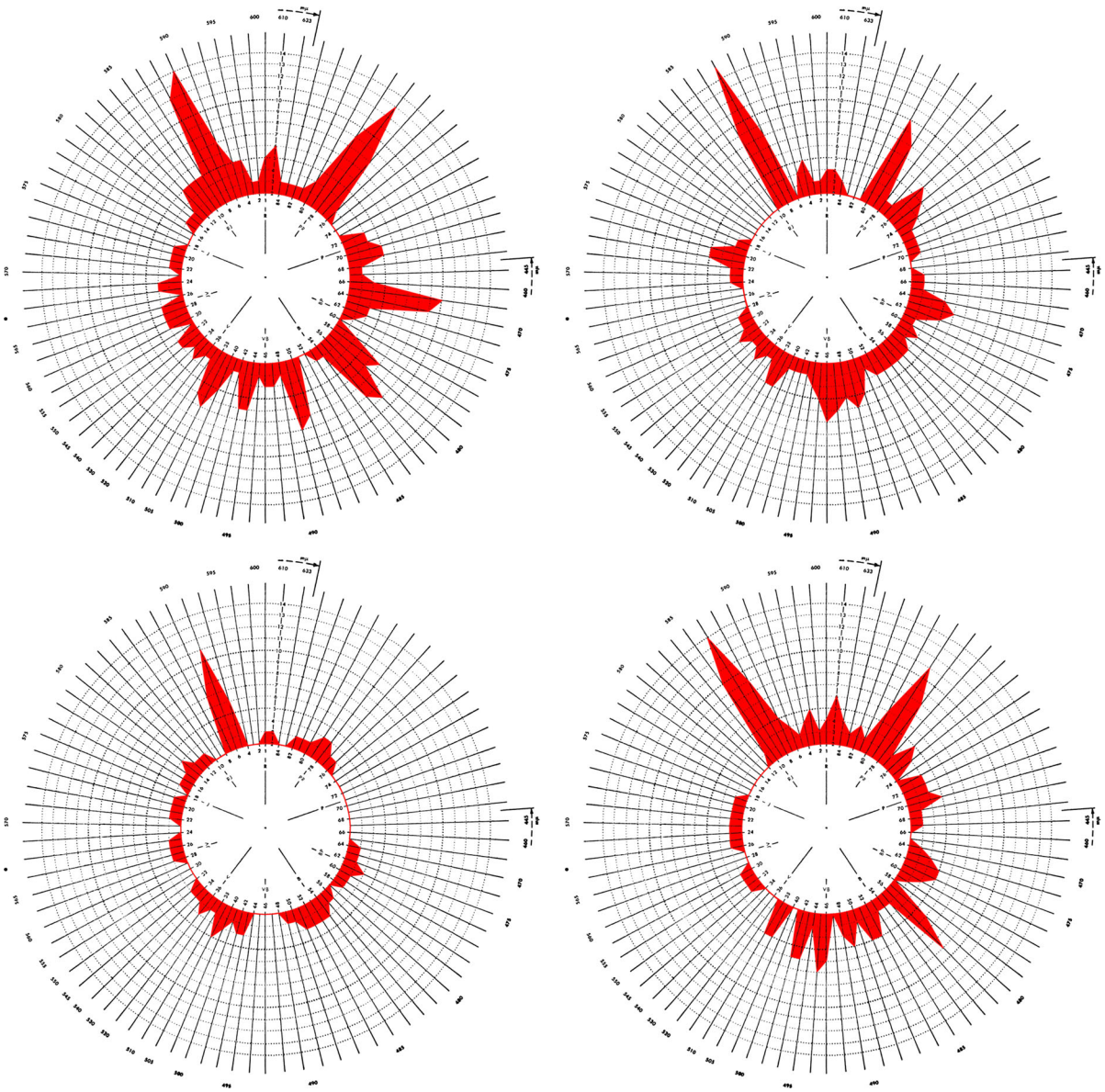

Fig. 2 Farnsworth 100 Hue color test. *Top* patient 1, *bottom* patient 2. Right eye on the *right* and left eye on the *left*. Tritan axis with a "swallow-tail" in *reddish* sectors and neighbor transpositions

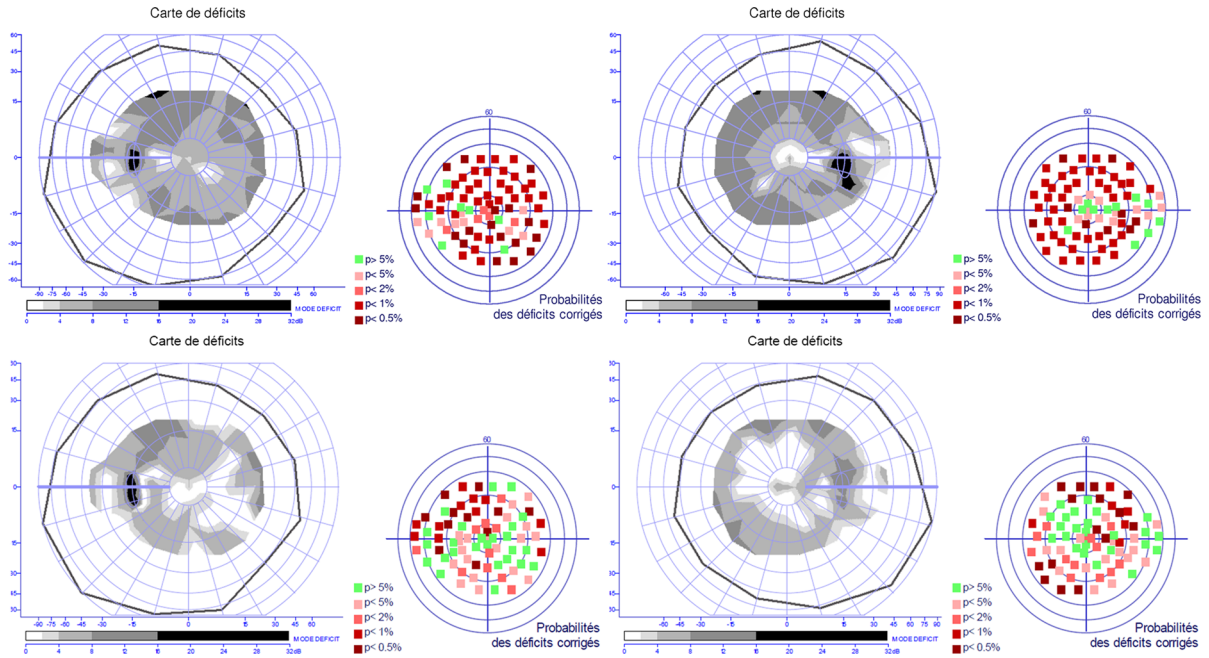

Fig. 3 Initial static perimetry. Visual fields showed reduced foveal threshold along with a ring-shaped scotoma in both eyes in patients 1 (*top*) and 2 (*bottom*)

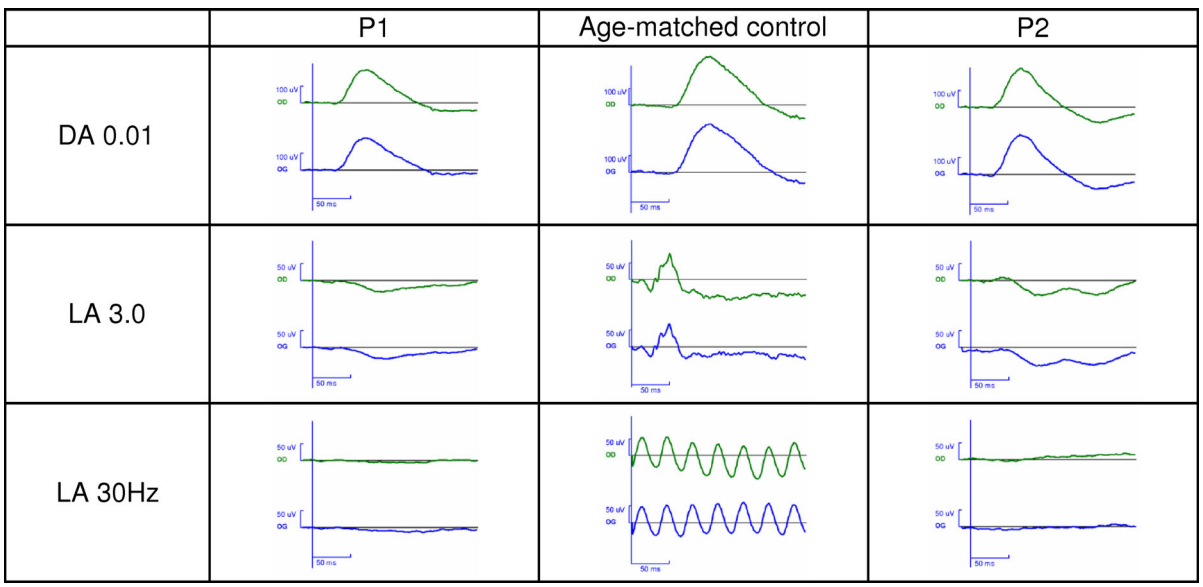

Fig. 4 ERG at initial presentation in 1994. The rod-specific ERG (DA 0.01) is normal. The light-adapted cone response (LA 3.0) as well as 30-Hz flicker (LA 30 Hz) is abolished. P1 and P2: patients 1 and 2, respectively

Farnsworth 100 Hue showed an increased error score [4] compared to age-matched controls (Table 1). Although a diffuse color discrimination problem was predominant, careful examination might suggest a tritan axis with a "swallow-tail" in reddish sectors (Fig. 2), already described in some patients with OT [5]. Visual fields demonstrated a reduced foveal threshold along with a ring-shaped scotoma around

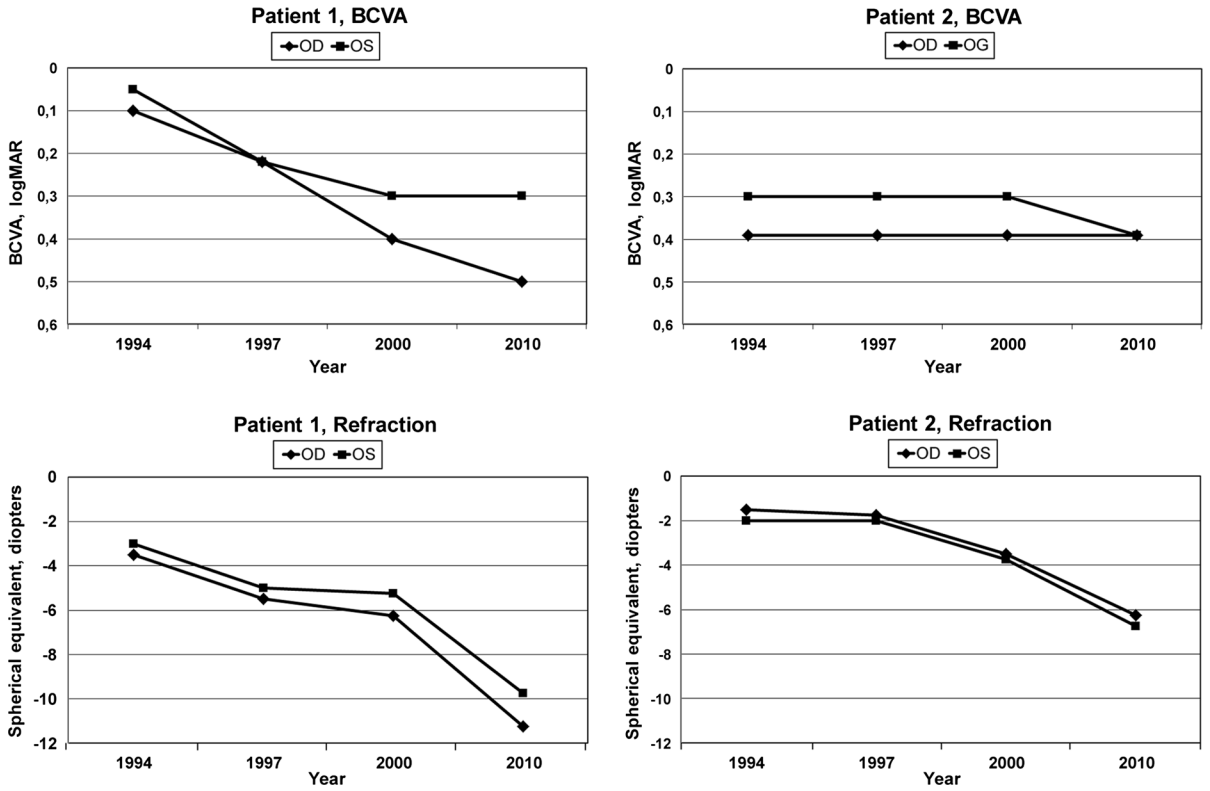

Fig. 5 *Top* course of the visual acuities (VA). VA decreased gradually in patient 1 in both eyes, and in patient 2's left eye. *Bottom* course of the spherical equivalent refraction. The course of refraction shows a progressive myopic shift in both patients

fixation (Fig. 3). Full-field ERG showed typical features of OT with normal scotopic system and abolished cone response after light adaptation and to 30-Hz flicker (Fig. 4). Genetic testing did not detect any mutations consistent with achromatopsia.

Follow-up

Follow-up examinations showed gradually decreased visual acuities, along with a progressive myopic shift (Fig. 5) and subtle macular pigmentary changes in both patients. Color vision using saturated color tests remained normal in both patients, but patient 1 had mild degradation of the error score on the 100 Hue of Farnsworth (Table 1). Visual fields (Fig. 6) and ERGs (Fig. 7) were overall unchanged. The rod-specific ERG remained normal. The dark-adapted maximal response was slightly decreased with biphasic b-wave. The light-adapted cone response as well as 30-Hz flicker was abolished. The responses to long-duration stimuli had a peculiar appearance with no ON response, but a well-preserved OFF response; in addition, an a-wave of reduced amplitude was recorded. There was no cone response on the dark-adapted red flash. Initial OCT in 2010 demonstrated a thickening of the outer limiting layer with interruption of the foveal ellipsoid line, the feature of which has been previously reported in achromatopsia [6]. There was a parafoveal retinal thinning without interruption of any layer (Fig. 8).

Discussion

OT belongs to a heterogeneous group of non-progressive cone disorders [7], also including achromatopsia, blue cone monochromatism, Bornholm eye disease, and cone monochromatism. Our patients had all features of OT, including visual impairment, mild photophobia, most importantly cone dysfunction, and near-to-normal color vision. This discrepancy between profound cone dysfunction and relatively

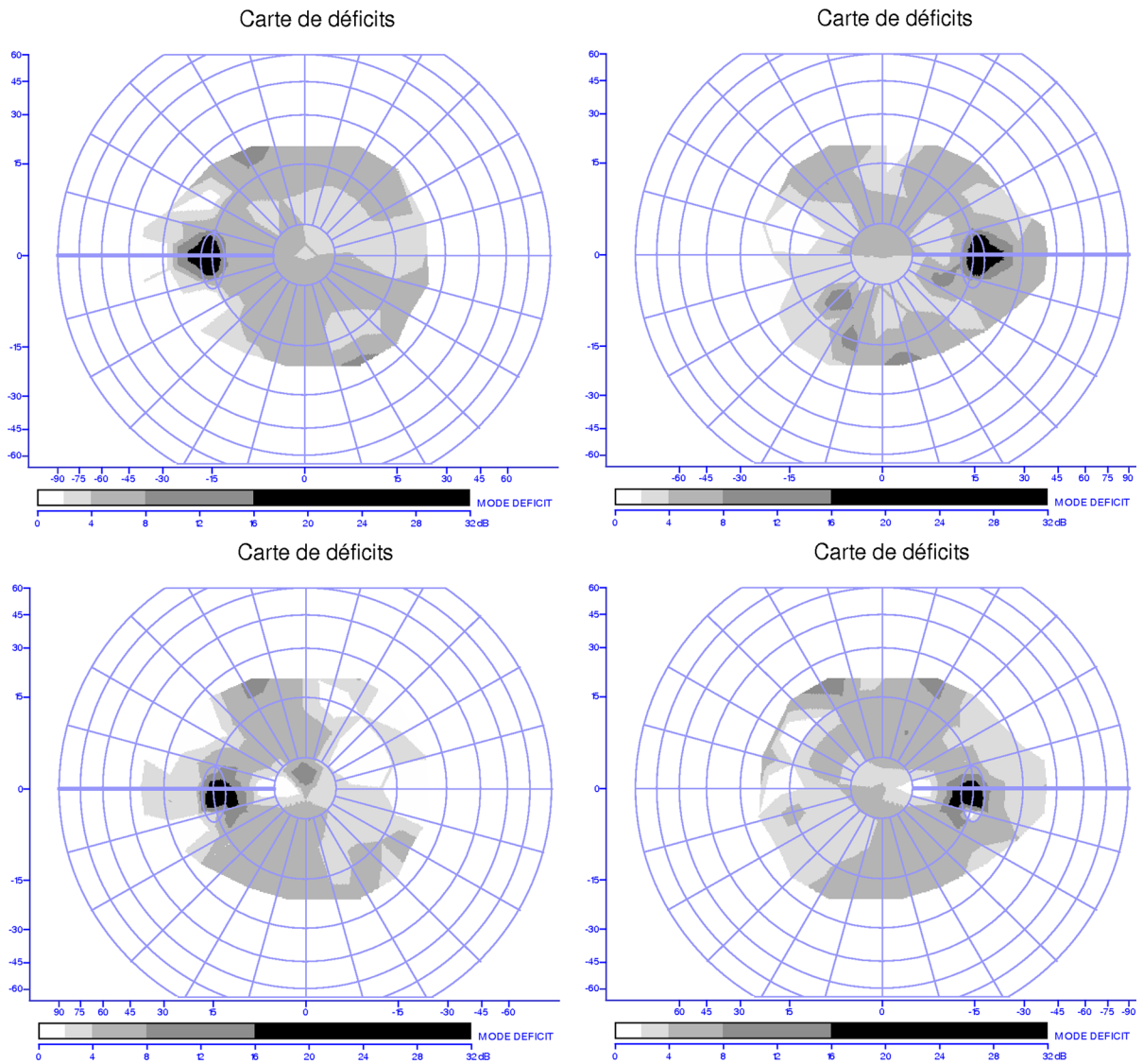

Fig. 6 Visual fields in 2010. *Top* patient 1, *bottom* patient 2. No changes

preserved color vision is one of the major criteria of OT [1, 8].

Although OT has been thought to be non-progressive in nature [8], our results might not support this clinical understanding, as repeat examinations over 18 years in our patients have shown subtle, yet inconsistent, worsening of visual function, including color vision in one patient and visual acuities in both of them. However, visual fields remained overall unchanged, which is likely related to the lack of sensitivity of our perimetry protocol to reveal subtle visual function changes around fixation. Full-field ERGs also remained stable, but we did not expect any changes over time, given that the cone system response was undetectable at initial presentation. From a structural standpoint, we showed subtle macular pigmentary changes over time in both patients on fundus examinations that might account for the subtle degradation of visual function. However, we failed to demonstrate any OCT changes, likely related to the very short OCT follow-up (2 years).

The underlying mechanism of OT remains poorly understood. Functionally, the discrepancy between the profound cone dysfunction and the near-to-normal

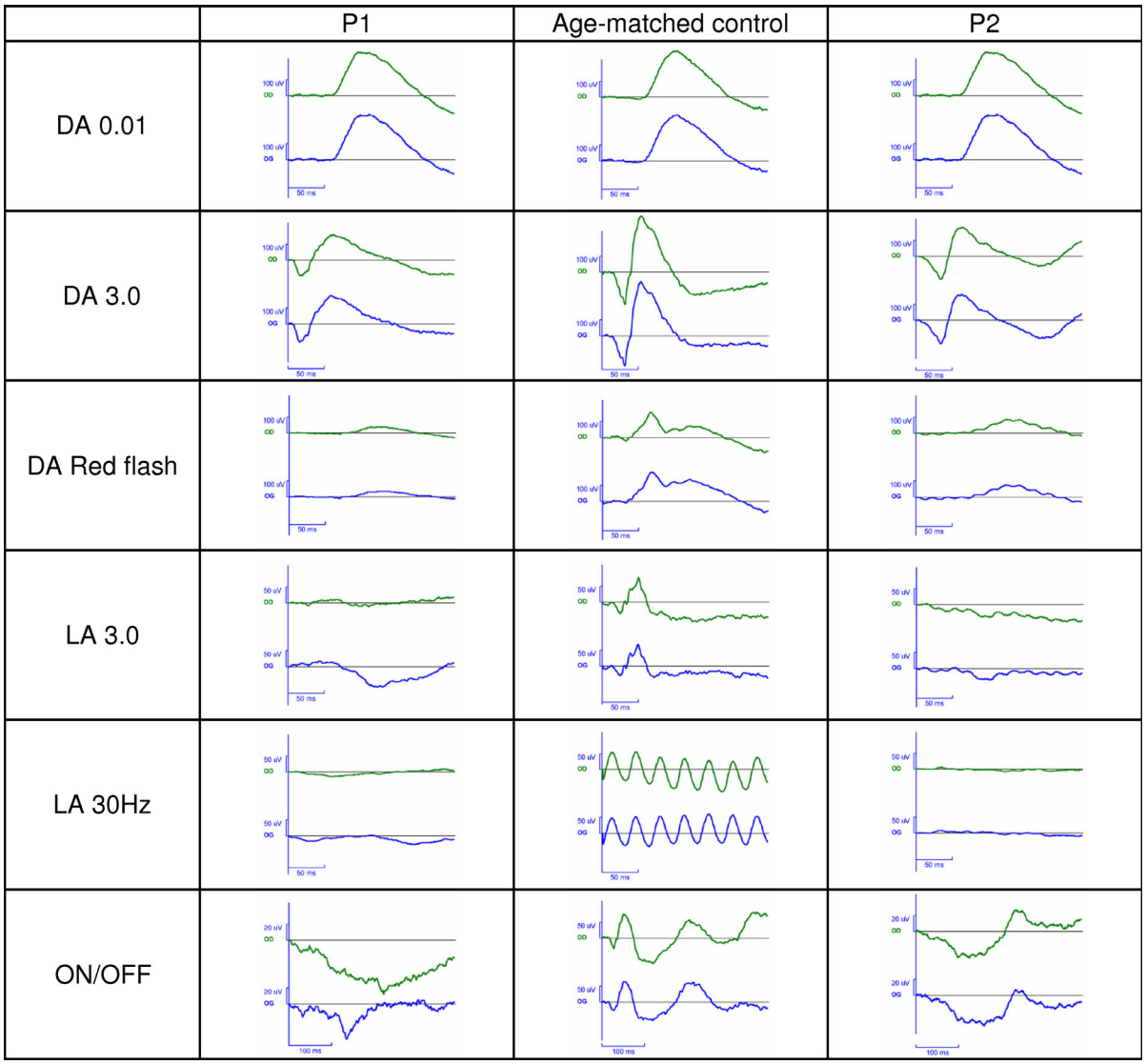

Fig. 7 ERG in 2000. The rod-specific ERG (DA 0.01) is normal. Dark-adapted maximal response (DA 3.0) was slightly decreased with biphasic b-wave. There is no cone response on the dark-adapted red flash (DA red flash). The light-adapted cone response (LA 3.0) as well as 30-Hz flicker (LA 30 Hz) is abolished. ON–OFF ERG: no ON response but a well-preserved OFF response; an a-wave of reduced amplitude was recorded. P1 and P2: patients 1 and 2, respectively

color discrimination with relative sparing of visual acuity would suggest primary involvement of the extrafoveal cones, as previously suggested [5] and highlighted in our study by the ring-shaped scotoma around fixation on visual fields along with decreased parafoveal retinal thickness. Interestingly, our patients had alterations of the "ON" response with relative preservation of the "OFF" response, suggesting an "ON" pathway involvement and perhaps post-receptor processing abnormalities [8]. Surprisingly, we were able to record an a-wave, albeit of reduced amplitude, in our patients, likely explained by the fact that the a-wave arises partially from the OFF bipolar cell hyperpolarization [9].

OT is thought to be a recessive autosomic genetic disorder [10], and the pedigree of our patients is consistent with such transmission. While a wide range of mutations has been identified in other cone dysfunctions, including achromatopsia (CNGA3, CNGB3, GNAT2, and PDE6C) and cone dystrophy

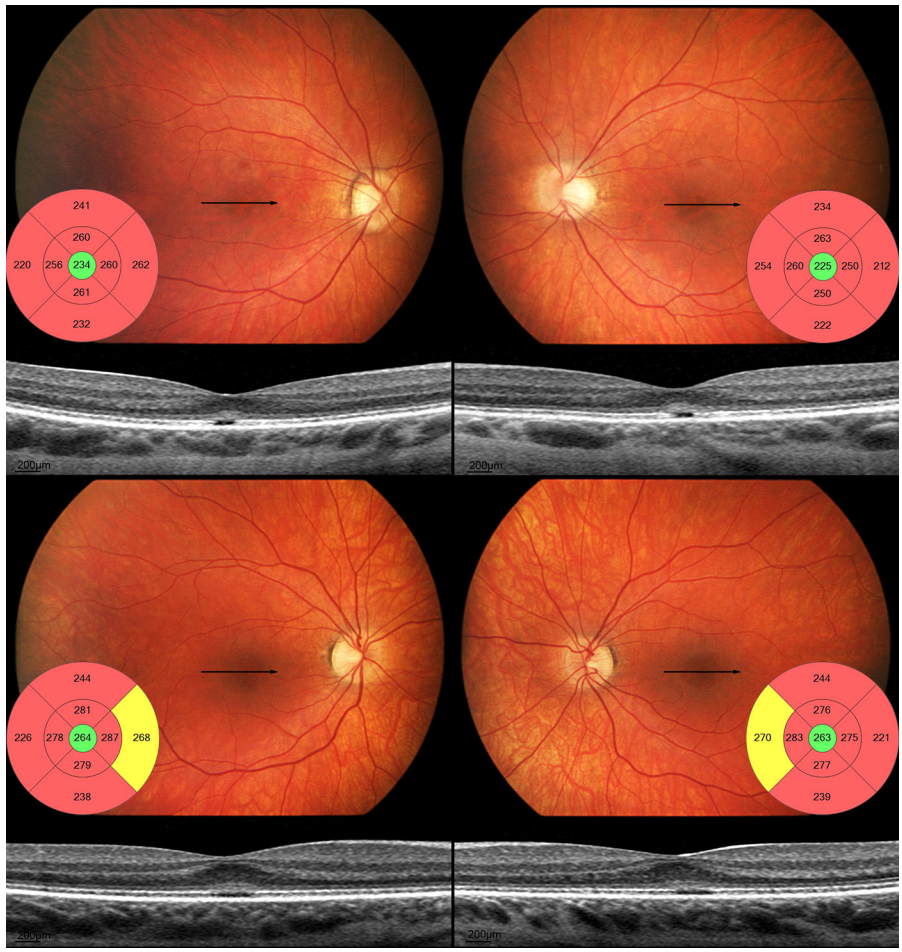

Fig. 8 Fundus photographs and macular OCT in 2010. There are subtle macular pigmentary changes. OCT shows a focal subfoveal interruption of *ellipsoid line* as it seen in achromatopsia. Parafoveal retinal thinning in both patients. Patient 1 at the *top*, patient 2 at the *bottom*

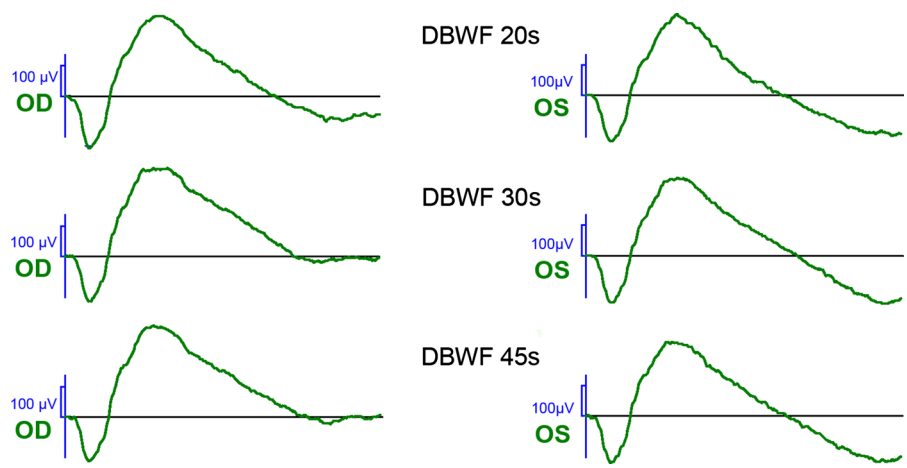

Fig. 9 Recovery of photoreceptoral function. A double-flash dark-adapted response with variation of interstimulus interval shows no increase in a- and b-wave amplitude unlike in bradyopsia. Only patient 2 had this examination

(ABCA4, CNGA3, CNGB3, and PDE6C), we and previous reports have failed to identify any mutations in OT [8]. Further direction might focus on genes involved with retinal photoreceptor differentiation [8].

Differential diagnoses include incomplete achromatopsia and bradyopsia [10], neither of which was consistent with clinical presentations reported here. Patients with achromatopsia [7] and OT do have similar ERG patterns, but individuals with achromatopsia report intense photophobia, and ocular examination shows nystagmus and profound loss of color discrimination. In addition, mutations in CNGA3 and PDE6C genes have been associated with incomplete achromatopsia [10], but not with OT. Patients with bradyopsia [11–13] experience difficulties with light–dark transition, with better visual acuity in scotopic condition using a pinhole. In addition, their disability at perceiving moving target is a striking feature of patients with bradyopsia. Our patients reported none of these symptoms. Both scotopic and photopic responses are markedly reduced in bradyopsia, with normal scotopic response to red stimuli [10, 14]. A specific ERG feature of patients with bradyopsia using the dark-adapted 0.8 log double-flash protocol with variation of the interstimulation interval reveals increased and full recovery of the response if the interstimulation interval is longer than 30 s [15]. This kind of recovery was not observed in our patients (Fig. 9). RGS9 and R9AP mutations have been associated with bradyopsia [16], but screening for such mutations was not available at our institution.

Conclusion

OT is an emergent, albeit controversial, concept that remains poorly understood in terms of nosology and pathophysiology, but might belong to a spectrum of cone disorder with a wide range of clinical presentations [1, 5, 17, 18]. Whereas OT has been known as a non-progressive disease, our results suggest that careful examination over a long period of time might reveal subtle worsening of the visual function. Further investigation regarding visual outcome should focus on clinical correlations with OCT changes over a longer period of time.

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Compliance with Ethical Standards

Conflict of interest None.

Patient consent The patients have consented to the submission of the case report to the journal.

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